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EFFECT OF NICKEL AS A TRACE ELEMENT ON THE ACTIVITY OF CYTOCHROME OXIDASE AND SUCCINATE DEHYDROGENASE IN VARIOUS ORGANS

[Vliyaniye nikelya kak mikroelementa na aktivnost' tsitokhromoksidazy i suktsindegidrogenazy v razlichnykh organakh]

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EFFECT OF NICKEL AS A TRACE ELEMENT ON THE ACTIVITY OF CYTOCHROME OXIDASE AND SUCCINATE DEHYDROGENASE IN VARIOUS ORGANS

One of the groups of cofactors in the presence of which the effect of many enzymes appears is the activators. This group includes the trace elements. Over one-fourth of all known enzymes (180 of 660) are metalloenzymes. Nineteen true metalloenzymes are known, and are characterized by a strong bond between the protein carrier of the enzymes and a definite metal. All the other metalloenzymes form metalloenzyme complexes in which the metal is readily separated from the protein carrier. In cases such as these, the enzyme can be reactivated by other metals as well.

Among the true metalloenzymes are succinate dehydrogenase and cytochrome oxidase, specifically with respect to iron. Nickel ions usually will not bond with proteins, and there are no known enzymes, specifically with respect to this metal, at this time. However, the fact of the bonding of nickel with RNA has been disclosed [5]. The nonspecific activation by nickel ions has been shown with respect to yeast phosphatase, unpurified arginase, and peptidases. These enzymes can be activated by metals other than nickel. This is so in the case of yeast phosphatase, for example, by Mg^{++}, Mn^{++}, Co^{++}, Fe^{++}, and Ni^{++} [4]. The reactivation of true metalloenzymes has been noted as well. The inclusion in the composition of apocarboxypeptidase A of Zn, as well as of Co, Ni, Mn, and Fe, will cause it to reactivate, while cobalt and

nickel containing artificial choloenzymes exceed in their activity that of natural carboxypeptidase [3].

The question of the effect of nickel on the activity of cytochrome oxidase and of succinate dehydrogenase is of interest in view of the foregoing, and elucidation would make it possible to form an opinion as to change in the oxidative and reducing powers of the different organs and tissues of a living organism injected with nickel salts.

A study of the influence of nickel on the activity of enzymes was made in May-July 1966, in the Department of Normal Physiology at the Turkmen Medical Institute. The zonality of the effect of the trace element was taken into consideration in our work [1].

Methodology. We used the methodology in use in Professor V. M. Vasyutochkin's laboratory to determine the activity of cytochrome oxidase and succinate dehydrogenase. The colorimetric determination of the activity of cytochrome oxidase was based on the oxidation of α-naphthol and dimethyl-para-phenylenediamine by cytochrome oxidase in indophenol blue. At the basis of determination of the activity of succinate dehydrogenase was the reduction of triphenyltetrazole chloride, or of neotetrazole chloride, in red formazan, and then submitting it to colorimetry.

The experiments were performed on guinea pigs given a spring water solution of nickel chloride ($NiCl_2 \cdot 6H_2O$) perorally at the rate of 2 milliliters twice a day for from 5 to 7 days. The nickel dosage was tested over a broad range; 0.5, 20, and 800 micrograms, 32 milligrams, and 1.28 grams per kilogram of animal weight per day in terms of the metal. Spring water

only was administered to the control group of animals. The animals were slaughtered after the designated period of time had elapsed. The activity of the cytochrome oxidase and of the succinate dehydrogenase was determined in the brain (subcortical part), liver, spleen, cortical layer of the kidneys, and muscles. One hundred eleven guinea pigs were used in the experiments, and of these these 24 were set aside as a control group. Tables 1 and 2 list the results of the study.

TABLE 1. CHANGE IN THE ACTIVITY OF CYTOCHROME OXIDASE (in µg of indophenol blue) AS INFLUENCED BY DIFFERENT DOSES OF NICKEL CHLORIDE

Organs	Control	Nickel chloride dosage (kgw/d)				
		0,5 µg	20µg	800 µg	32 mg	1,28 g
Brain						
M	1107,000	1130,000	1094,000	1109,000	1084,000	1090,000
m	7,550	9,010	8,550	8,920	9,560	12,090
%	100,000	103,000	99,700	101,100	98,800	99,300
P <	—	0,001	0,300	0,500	0,500	0,100
Liver						
M	813,000	858,000	792,000	726,000	760,000	833,000
m	15,410	24,070	18,560	20,750	12,090	23,190
%	100,000	105,100	97,400	89,300	93,500	91,500
P <	—	0,001	0,300	0,001	0,001	0,500
Spleen						
M	249,000	251,000	253,000	243,000	242,000	199,000
m	10,400	9,840	7,550	6,120	10,390	5,420
%	100,000	102,500	101,300	99,200	98,800	81,200
P <	—	0,200	0,100	0,500	0,500	0,001
Kidneys						
M	1160,000	1196,000	1175,000	1165,000	1133,000	1062,000
m	8,980	11,440	15,900	14,400	11,000	23,500
%	100,000	103,100	101,300	100,400	97,700	89,800
P <	—	0,001	0,500	0,200	0,001	0,001
Muscles						
M	721,000	745,000	825,000	714,000	803,000	838,000
m	33,290	29,300	37,400	54,500	45,000	41,200
%	100,000	101,200	114,500	98,300	110,600	115,500
P <	—	0,200	0,001	0,200	0,200	0,001

TABLE 2. CHANGE IN THE ACTIVITY OF SUCCINATE DEHYDROGENASE (in µg of formazan) AS INFLUENCED BY DIFFERENT DOSES OF NICKEL CHLORIDE

Organs	Control	Nickel chloride dosage (kgw/d)				
		0.5 µg	20 µg	[illegible] µg	32 mg	1.28 g
Brain						
M	39,500	44,120	39,750	39,550	36,710	37,400
m	1,680	1,320	1,600	1,700	1,420	?,640
%	100,000	109,200	100,600	[illegible],100	93,000	95,000
P <	—	0,050	0,200	0,500	0,100	0,200
Liver						
M	151,700	179,800	163,300	[illegible],300	141,600	150,400
m	6,300	8,200	7,650	6,530	5,840	6,600
%	100,000	118,400	107,800	[illegible],400	93,300	99,100
P <	—	0,020	0,500	0,500	0,500	0,300
Spleen						
M	113,200	117,000	115,500	112,100	114,400	102,000
m	5,160	5,820	5,280	2,550	6,400	5,450
%	100,000	103,400	100,[illegible]10	[illegible],000	101,000	90,100
P <	—	0,200	0,[illegible]50	0,500	0,500	0,200
Kidneys						
M	73,500	88,100	70,700	71,800	63,800	57,900
m	3,630	5,500	4,800	2,650	2,900	2,610
%	100,000	119,900	96,200	[illegible],700	86,800	78,800
P <	—	0,001	0,500	0,500	0,001	0,001
Muscles						
M	22,000	22,900	27,500	25,900	26,800	25,500
m	1,600	1,520	2,150	2,410	2,330	3,130
%	100,000	101,300	121,700	[illegible],600	118,600	112,800
P <	—	0,500	0,010	0,100	0,100	0,200

As may be seen from Tables 1 and 2, changes in the activity of cytochrome oxidase and succinate dehydrogenase, as influenced by nickel chloride, are more pronounced in the case of the latter, but changes are somewhat different in the activity of the enzymes in the different organs.

Small quantities of nickel (0.5 µg per kg of animal weight per day) increased the activity of cytochrome oxidase in the subcortex, cortex of the kidneys, and liver. This same dose of nickel resulted in a similar effect with respect to the activity of succinate dehydrogenase in these same organs. The increase in the activity of both enzymes in the spleen

falls within the limits of variability for the phenomenon. There is practically no change in the activity of the enzymes in the muscles, but increasing the daily dose of nickel to 20 µg/kg does show a sharp effect in both cases. This dose had no effect on the other organs, with the exception of that of cytochrome oxidase in the liver, the activity of which fell below the figure for the control, and even further below that of the control when the nickel dose was increased to 800 µg/kg. The latter proved to be ineffective in virtually all cases, with the exception of liver cytochrome oxidase, the activity of which fell off (to 89.3%). A nickel dose of 32 mg/kg inhibited the activity of cytochrome oxidase in the liver, cortex of the kidneys, and subcortex, but only slightly in the spleen. There was a sharp inhibition of succinase dehydrogenase in the kidneys, but the inhibition was less sharp in the liver and subcortex.

Nickel chloride was highly toxic when used in a dose of 1.28 g/kg. Two of the 15 animals in this group that received the nickel fell on the second and third days, and 2 on the fourth day of taking nickel. Study of the activity of the enzymes in the rest of the animals of this group revealed a further reduction in the activity of the cytochrome oxidase in the kidneys, and a particularly sharp reduction in the spleen and, what is interesting, there was a sharp inhibition of the activity of the succinate dehydrogenase in the kidneys as well. This same dose of nickel caused some increase in enzyme activity (as compared with that for the 32 mg/kg dose) in the liver and subcortex.

The The activity of the enzymes in the muscles was increased by small

(20 µg/kg) as well as large (32 mg/kg and 1.28 g/kg) doses of nickel, but there was a reduction in the activity when the dose was 800 µg/kg.

The data listed in Tables 1 and 2 indicate the zonality of the effect of nickel as a trace element. The use of nickel in doses approximately equal to the content of this metal in the body (the mean concentration of nickel in animal bodies is 0.001 mg%)[2] does not, it should be assumed, evoke a protective reaction by the body's barrier system (the wall of the intestine, lymph nodes), with the result that the nickel is unhampered in finding its way into the organs and tissues of the animal body with the blood, leading to unspecific activity of cytochrome oxidase and succinate dehydrogenase in these organs. This biotic effect of small doses of nickel (0.5 µg/kg for the brain, liver, and kidneys, and 20 µg/kg for the muscles) is separate from the toxic effect of large doses of nickel for the zone of inactivity (doses of 20 µg/kg and 800 µg/kg), in accordance with which the activity of the enzymes indicated undergoes no significant change.

CONCLUSIONS

1. A daily peroral administration to guinea pigs of solutions of nickel chloride over a period of from 5 to 7 days in doses of 0.5 µg/kg/d increases the activity of cytochrome oxidase and succinate dehydrogenase in the subcortical part of the brain, liver and cortex of the kidneys ($P < 0.05 - 0.001$), and, in a dose of 20 µg/kg in the muscles ($P < 0.01 - 0.001$) (the zone of biotic activity).

2. Given these experimental conditions, the use of nickel in doses of 20 µg/kg and 800 µg/kg results in no variational, statistically reliable

change in enzyme activity (zone of inactivity).

3. The use of nickel in doses of 32 mg/kg and 1.28 g/kg results in inhibition of the activity of both enzymes in the cortex of the kidneys ($P < 0.001$), and of cytochrome oxidase in the liver and spleen, as well as to an increase in the activity of cytochrome oxidase in the muscles (zone of toxic-pharmacological activity).

4. The effect of nickel on the activity of the enzymes in the different organs manifests itself in different ways. The maximum biotic effect is observed in the kidneys and muscles, and the maximum toxic effect in the kidneys, and in the spleen when large doses are used.

5. The change in enzyme activity caused by nickel is better defined in succinate dehydrogenase than in cytochrome oxidase.

6. Nickel chloride acts as an activator, or as an inhibitor, depending on the dose used when administered to guinea pigs perorally, leading to an unspecific change in the activity of cytochrome oxidase and succinate dehydrogenase in different tissues.

Turkmen Medical Institute Submitted 27 June 1967

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